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Multicomponent Reaction Based Synthesis of 1-Tetrazolylimidazo[1,5-*a*]pyridines

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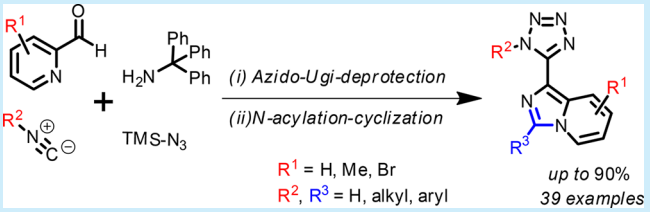
Supporting Information

ABSTRACT: A series of unprecedented tetrazole-linked imidazo[1,5-*a*]pyridines are synthesized from simple and readily available building blocks. The reaction sequence involves an azido-Ugi-deprotection reaction followed by an acetic anhydride-mediated *N*-acylation−cyclization process to afford the target heterocycle. Furthermore, the scope of the methodology was extended to diverse R_3-substitutions by employing commercial anhydrides, acid chlorides, and acids as an acyl component. The scope for the postmodification reactions are explored and the usefulness of the synthesis is exemplified by an improved three-step synthesis of a guanylate cyclase stimulator.



The design and synthesis of new bis-heterocyclic systems are highly appreciated in modern drug discovery to achieve specific drug−receptor interactions.[1] Tetrazole-linked imidazo[1,5-*a*]pyridine is such an unprecedented class of bis-heterocycles. Individually, the imidazo[1,5-*a*]pyridine heterocycle is the core of naturally occurring antimicrobial and antineoplastic agent cribrostatin 6[2] as well as many bioactive molecules, for example 5-hydroxytryptamine$_4$ receptor (5-HT4R) antagonists[3] and partial agonists,[4] CB2 agonists,[5] HIV protease inhibitors,[6] thromboxane A_2 synthesis inhibitors,[7] and guanylate cyclase stimulators.[8] It has also found applications in material chemistry,[9] and 1,5-disubstituted tetrazoles (1,5-DS-T's) are bioisosteres of the *cis*-amide bond of peptides,[10] which are present in various drugs,[11] such as cilostazol and the antibiotics cefonicid and latamoxef.[12] However, a combination of the two well-known imidazo[1,5-*a*]pyridine and 1,5-DS-T into a bis-heterocyclic systems has not been explored much in medicinal chemistry due to limitations in synthetic feasibility (Figure 1). To the best of our knowledge, only Schirok et al. have reported a seven-step synthesis of guanylate cyclase stimulator 3-(2-fluorobenzyl)-1-(1*H*-tetrazol-5-yl)imidazo[1,5-*a*]pyridine **9**, starting from ethyl 2-(pyridin-2-yl) acetate with 1.8% overall yield (Scheme 2).[8] Therefore, developing more practical and efficient synthetic approaches for tetrazole-linked imidazo[1,5-*a*] pyridines is highly desirable. Our synthetic strategy for such a bis-heterocyclic system involves the Ugi-azide four component reaction (azido-Ugi 4CR)-deprotection to obtain the corresponding pyridin-2-yl(1*H*-tetrazol-5-yl)methanamine intermediate.[13] The intermediate amine is then converted to tetrazolyl-imidazo[1,5-*a*]pyridine via an *N*-acylation−cyclization process (Figure 1).[14]

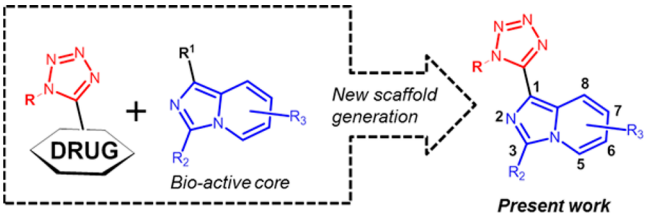


Figure 1. Conceiving the idea.

Thus, we describe the Ugi-azide four-component reaction (azido-Ugi 4CR) mediated synthesis of diverse analogues of 1-tetrazolylimidazo[1,5-*a*]pyridines.

Example **6a** (Table 1, entry 1a) was selected as a model for screening and optimizing the reaction conditions. Equimolar amounts of aldehyde (**1**, R^1 = H), tritylamine **2**, isocyanide (**3**, R^2 = benzyl), and azidotrimethylsilane **4** were combined sequentially in MeOH (0.5 M) at room temperature. The corresponding azido-Ugi product **5** was isolated in high yield of 85% after 18 h. Trityl group removal under acidic conditions (4 N HCl/dioxane) gave the (1-benzyl-1*H*-tetrazol-5-yl)(pyridin-2-yl)methanamine hydrochloride. We then tested the cyclization reaction under different reaction conditions using Ac_2O to form **6a**. We screened several conditions and varyied reaction parameters such as temperature, base, and Ac_2O concentration. To our surprise, no base was required, only Ac_2O (0.5 M) and warming (75 °C). A reaction time of 1 h was found to be optimal, with **6a** being isolated in quantitative yield. With these optimized conditions in hand, we decided to switch to a one-pot protocol to avoid the isolation of the azido-Ugi intermediate. Here, the generally observed precipitation of trityl Ugi-azides

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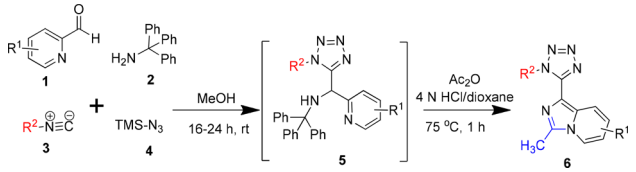
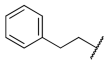
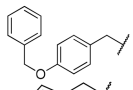
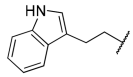
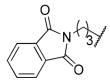
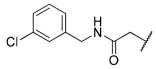
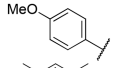
Table 1. Substrate Scope of the 1-Tetrazolyl-3-methylimidazo[1,5-*a*]pyridine Synthesis



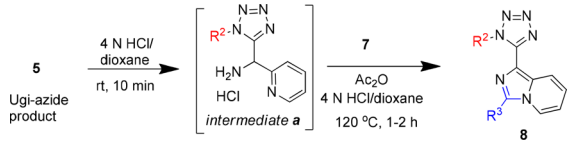
Entry[a]	Aldehyde **1** R_1	Isocyanide **3** R_2	Product **6**	Yield(%)[b]
1a	H		**6a**	85
1b	H		**6b**	88
1c	H		**6c**	82
1d	H		**6d**	75
1e	H		**6e**	87
1f	H		**6f**	80
1g	H		**6g**	65[c]
1h	H		**6h**	90
1i[d]	H		**6i**	60
1j	H		**6j**	75
1k	H		**6k**	77
1l	6-Me		**6l**	78
1m	5-Br		**6m**	74

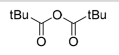
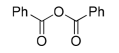
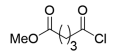
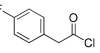
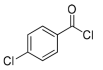
[a]Reaction scale 1.0 mmol. [b]Isolated yield. [c]Indole *N*-acylated product was isolated in 15% yield. [d]Azide–Ugi product (5) was isolated in 62% yield along with tetrazole regioisomeric product 20% yield.

was of great help. The azido-Ugi product **5** was quickly isolated by filtration to remove the solvent methanol and subjected to cyclization without any further purification with 4 N HCl/dioxane (3.0 equiv), Ac_2O [0.5 M] at 75 °C for 1 h, affording **6a** in 85% overall yield. The reaction proceeds via in situ trityl deprotection followed by Ac_2O-mediated *N*-acylation–cyclization to form **6a**. Using the optimized conditions, we next synthesized a series of novel 1-tetrazolyl-3-methylimidazo[1,5-*a*]pyridines **6b–m** in a one-pot, two-step manner (Table 1, entries 1b–m). The scope of the substrate was evaluated using diverse isocyanides (**3**) and picolinaldehydes (**1**). Overall good to excellent yields were obtained. The highest yield of 90% was observed for product **6h** (Table 1, entry 1b). Additionally, a lower yield was observed for the product **6g** (65%, entry 1g) and **6i** (60%, entry 1d).

Encouraged by the initial results, we investigated more diverse synthesis by changing the R_3-substitutions on tetrazolylimidazo-[1,5-*a*]pyridine core **8** according to our two-step procedure. Accordingly, step 1 involved the trityl deprotection of the azido-Ugi 4CR product **5** under acidic conditions (4 N HCl/dioxane, 10 min) to give the corresponding intermediate pyridin-2-yl(1*H*-tetrazol-5-yl)methanamine (intermediate **a**) as a HCl salt.[13] In step 2, intermediate **a** was *N*-acylated using **7** as a commercial anhydride or acid chloride in DCM and NEt_3 (2.2 equiv) as a base; in the case of acids, classical peptide coupling conditions EDC, HOBt, and NEt_3 in DCM were used.[15] Then the in situ formed corresponding *N*-acyl intermediate (without purification) was subjected to cyclization (1.0 equiv 4 N HCl/dioxane, Ac_2O [0.5 M], 120 °C, 1–2 h) after removal of DCM (Table 2, entries 2a–q). Anhydrides including cyclic glutaric

Table 2. R_3-Substitutions on Tetrazolylimidazo[1,5-*a*]pyridine



Entry[a]	R_2	**7**	R_3	Product **8**	Yield(%)[b]
2a				**8a**	85
2b				**8b**	78
2c				**8c**	70
2d				**8d**	87
2e				**8e**	85
2f				**8f**	80
2g				**8g**	82
2h				**8h**	70
2i				**8i**	85
2j[c]				**8j**	80
2k				**8k**	67
2l				**8l**	79
2m				**8m**	60
2n				**8n**	40
2o				**8o**	45
2p				**8b**	70
2q				**8q**	trace

[a]Reaction scale 1.0 mmol. [b]Isolated yield. [c]The reaction scale was 5.0 mmol; reaction mixture was heated at 75 °C for 8 h.

anhydride (entries 2a–c) worked well under the optimized conditions and produced **8a–c** in 70–85% overall yield. A diverse set of acid chlorides (entries 2d–i) as the acyl component worked well, and the corresponding products were formed in generally very good yield. We observed a drop in overall yields in the case of acids (40–79%, entries 2k–o) compared to anhydrides and acid chlorides, which may reflect worse coupling yields. In the case of *N*-Boc-protected amino

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acids, the corresponding *N*-acyl products **8m−o** (entries 2m−p) were isolated in 40−60% yields. Deborylation was observed in the case of the 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid, and **8b** was isolated with 70% yield. Thus, Boc and pinacol−borane groups were found to be labile under the optimized condition. In case of cyanoacetic acid, a trace amount of product **8q** was formed (Table 2, entry 2q).

Several structures have been confirmed by X-ray single-crystal analyses (Figure 2 and Supporting Information). The following

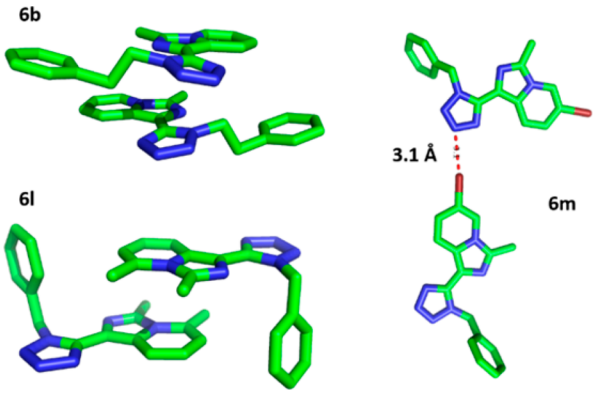
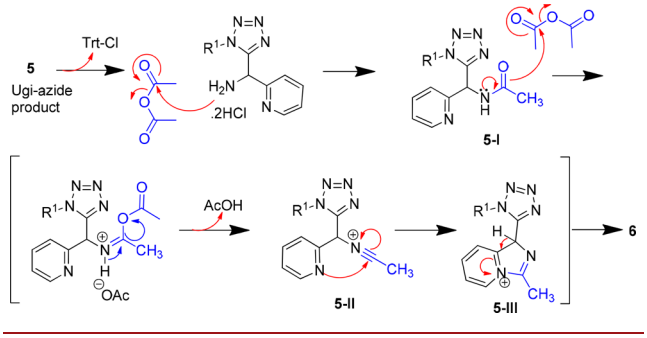


Figure 2. X-ray structures of selected products.

interesting motifs could be observed in the solid state: the scaffold in general is flat, and therefore, stocking interactions with neighboring molecules are always observed. In **6b** the tetrazole and in **6l** the imidazopyridine moieties stack antiparallel. In **6m**, a halogen bond with 3.1 Å between the *p*-Br and N_3 of an adjacent tetrazole can be found.

A mechanism is proposed in Scheme 1. The Azido-Ugi reaction mechanism has been documented.[13]

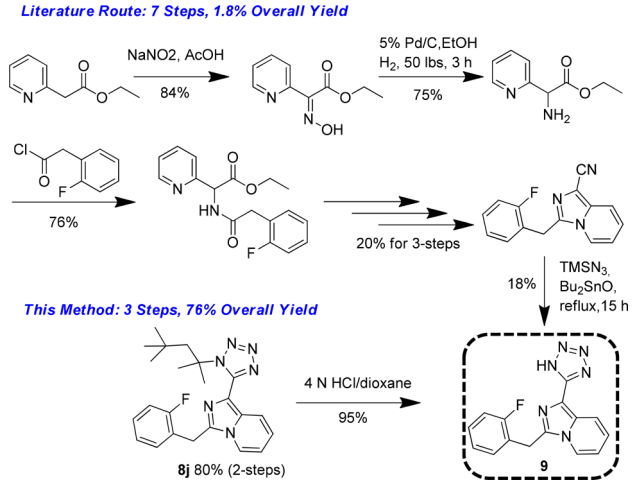
Scheme 1. Proposed Mechanism



Then the azido-Ugi product **5** undergoes *N*-acylation and forms intermediate **5-I** via acid-mediated trityl group deprotection. Further, **5-I** undergoes an O-acylation−elimination process and provides nitrilium intermediate **5-II**. Attacking the ring nitrogen lone pair of electrons from **5-II** leads to the cyclic intermediate **5-III**, which upon aromatization leads to the formation of the target product **6** (Scheme 1).

As an application of the methodology, we could improve upon the synthetic route of the guanylate cyclase stimulator **9** in three simple steps with 76% overall yield, via acid mediated tert-octyl group deprotection[13] of **8j** in the final step (Scheme 2). After demonstrating the successful synthesis of diverse substituted tetrazolylimidazo[1,5-*a*]pyridines, we wanted to further dem-

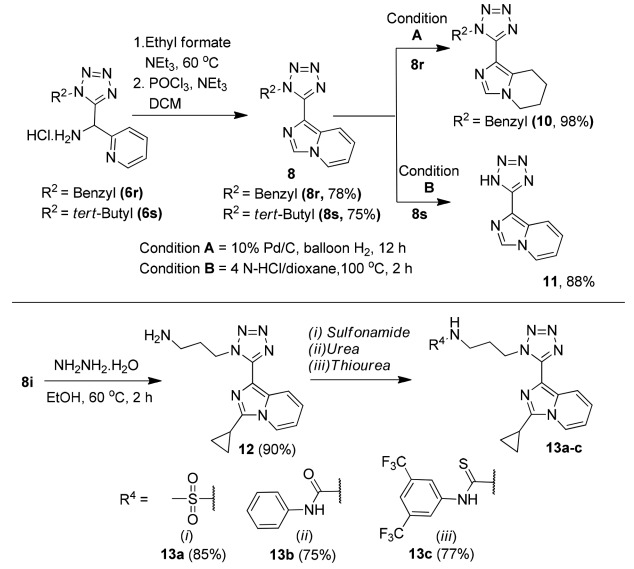
Scheme 2. Improved Route to the Guanylate Cyclase Stimulator (9)



onstrate the scope of the method by synthesizing unsubstituted (R_3 = H) examples and explore their postmodification.

Examples **8r** and **8s** were prepared from intermediates **6r** and **6s** in 74% and 78% yields, respectively, via one pot *N*-formylation followed by $POCl_3$-mediated dehydration−cyclization process (Scheme 3).[16] While attempting the debenzylation

Scheme 3. Postmodification Scope



of **8r** under hydrogenation condition, we observed the selective pyridyl ring saturation product, and **10** was isolated in 98% yield. The interesting low molecular weight free tetrazole **11** building block was obtained in 88% yield by deprotection of the *tert*-butyl group of **8s** under acidic conditions (Scheme 3).[17]

In continuation of exploring the post modification scope, the phthalimide group in **8i** was deprotected to form the free amine **12** (90% yield), which was subjected to three different types of reactions: (i) sulfonamide, (ii) urea, and (iii) thiourea formation.[18] All three types of reactions worked well and furnished the desired products **13a−c** in very good yields of 75−85% (Scheme 3).

Taken together, we have developed a novel, simple, and efficient two-step method for the synthesis of tetrazolylimidazo-

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[1,5-*a*]pyridines, a bis-heterocyclic system via the well-known azido-Ugi 4CR reaction, and an unprecedented acetic anhydride mediated post cyclization reaction. Work is ongoing to investigate the further synthetic applications and biological properties of the new compound class.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01452.

General procedures, characterization data, spectra (^{1}H,^{13}C NMR, HRMS), single crystal X-ray details (PDF)

Accession Codes

CCDC 1828260−1828262 and 1839326−1839329 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Bis- heterocyclic system and its applications: (a) Unnamatla, M. V. B.; Islas-Jácome, A.; Quezada-Soto, A.; Ramárez-López, S. C.; Flores-Ãlamo, M.; Gámez-Montaño, R. *J. Org. Chem.* **2016**, *81*, 10576−10583. (b) Murru, S.; Nefzi, A. *ACS Comb. Sci.* **2014**, *16*, 39−45. (c) Soural, M.; Bouillon, I.; Krchňak, V. *J. Comb. Chem.* **2008**, *10*, 923. (d) Kurhade, S.; Ramaiah, P. A.; Prathipati, P.; Bhuniya, D. *Tetrahedron* **2013**, *69*, 1354−1362. (e) Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* **1996**, *39*, 2887−2893.

(2) (a) Pelletier, G.; Charette, A. B. *Org. Lett.* **2013**, *15*, 2290−2293. (b) Pettit, G. R.; Collins, J. C.; Knight, J. C.; Herald, D. L.; Nieman, R. A.; Williams, M. D.; Pettit, R. K. *J. Nat. Prod.* **2003**, *66*, 544. (c) Mohamed, M.; Goncalves, T. P.; Whitby, R. J.; Sneddon, H. F.; Harrowven, D. C. *Chem. - Eur. J.* **2011**, *17*, 13698. (d) Knueppel, D.; Martin, S. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 2569. (e) Markey, M. D.; Kelly, T. R. *J. Org. Chem.* **2008**, *73*, 7441.

(3) King, F. D.; Gaster, L. M.; Joiner, G. F. Imidazopyridines and indolizines as 5-HT4 antagonists. PCT Pat. Appl. WO 1993/008187A1, 29 Apr 1993.

(4) Nirogi, R.; Mohammed, A. R.; Shinde, A. K.; Bogaraju, N.; Gagginapalli, S. R.; Ravella, S. R.; Kota, L.; Bhyrapuneni, G.; Muddana, N. R.; Benade, V.; Palacharla, R. C.; Jayarajan, P.; Subramanian, R.; Goyal, V. K. *Eur. J. Med. Chem.* **2015**, *103*, 289−301.

(5) Trotter, B. W.; Nanda, K. K.; Burgey, C. S.; Potteiger, C. M.; Deng, J. Z.; Green, A. I.; Hartnett, J. C.; Kett, N. R.; Wu, Z.; Henze, D. A.; Penna, K. D.; Desai, R.; Leitl, M. D.; Lemaire, W.; White, R. B.; Yeh, S.; Urban, M. O.; Kane, S. A.; Hartman, G. D.; Bilodeau, M. T. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2354−2358.

(6) Kim, D.; Wang, L.; Hale, J. J.; Lynch, C. L.; Budhu, R. J.; MacCoss, M.; Mills, S. G.; Malkowitz, L.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Hazuda, D.; Miller, M.; Kessler, J.; Hrin, R. C.; Carver, G.; Carella, A.; Henry, K.; Lineberger, J.; Schleif, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2129.

(7) Ford, F. F.; Browne, L. J.; Campbell, T.; Gemenden, C.; Goldstein, R.; Gude, C.; Wasley, J. W. F. *J. Med. Chem.* **1985**, *28*, 164.

(8) Schirok, H.; Mittendorf, J.; Stasch, J.-P.; Wunder, F.; Stoll, F.; Schlemmer, K.-H. Pyrazolopyridine, Indazole, Imidazopyridine, Imidazopyrimidine, Pyrazolopyrazine and Pyrazolopyridine derivatives as stimulator of guanylate cyclase for cardiovascular disorders. PCT Pat. Appl. WO 2008/031513 A1, 20 Mar 2008.

(9) (a) Shibahara, F.; Dohke, Y.; Murai, T. *J. Org. Chem.* **2012**, *77*, 5381. (b) Yamaguchi, E.; Shibahara, F.; Murai, T. *J. Org. Chem.* **2011**, *76*, 6146 and references cited therein.

(10) (a) Zabrocki, J.; Smith, G. D.; Dunbar, J. B., Jr.; Iijima, H.; Marshall, G. R. *J. Am. Chem. Soc.* **1988**, *110*, 5875−5880. (b) Rentería-Gómez, A.; Islas-Jacome, A.; Díaz-Cervantes, E.; Villaseñ or-Granados, T.; Robles, J.; Gamez-Montaño, R. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2333−2338.

(11) Drugs containing tetrazole moiety (review): Myznikov, L. V.; Hrabalek, A.; Koldobskii, G. I. *Chem. Heterocycl. Compd.* **2007**, *43*, 1−9.

(12) Ostrovskii, V. A.; Trifonov, R. E.; Popova, E. A. *Russ. Chem. Bull.* **2012**, *61*, 768−780.

(13) (a) Ugi, I.; Steinbruckner, C. *Angew. Chem.* **1960**, *72* (7−8), 267−268. (b) Zhao, T.; Boltjes, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2013**, *15*, 639−641. (c) Zhao, T.; Kurpiewska, K.; Kalinowska-Tłuścik, J.; Herdtweck, E.; Dömling, A. *Chem. - Eur. J.* **2016**, *22*, 3009. (d) Cioc, R. C.; Schuckman, P.; Preschel, H. D.; Vlaar, T.; Ruijter, E.; Orru, R. V. A. *Org. Lett.* **2016**, *18*, 3562−3565.

(14) (a) Pelletier, G.; Charette, A. *Org. Lett.* **2013**, *15*, 2290. (b) Crawforth, J.; Paoletti, M. *Tetrahedron Lett.* **2009**, *50*, 4916. (c) Arvapalli, V.; Chen, G.; Kosarev, S.; Tan, M.; Xie, D.; Yet, L. *Tetrahedron Lett.* **2010**, *51*, 284.

(15) Peptide coupling conditions: El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557−6602.

(16) (a) Gerack, C. J.; McElwee-White, L. *Molecules* **2014**, *19*, 7689−7713. (b) Ford, N. F.; Browne, L. J.; Campbell, T.; Gemenden, C.; Goldstein, R.; Gude, C.; Wasley, J. W. F. *J. Med. Chem.* **1985**, *28*, 164.

(17) Krasavin, M.; Tsirulnikov, S.; Nikulnikov, M.; Sandulenko, Y.; Bukhryakov, K. *Tetrahedron Lett.* **2008**, *49*, 7318.

(18) (a) For sulfonamide formation, see: Bahrami, K.; Khodaei, M. M.; Soheilizad, M. *J. Org. Chem.* **2009**, *74*, 9287−9291. (b) For urea and thiourea formation, see: Chayah, M.; Camacho, M. E.; Carrion, M. D.; Gallo, M. A.; Romero, M.; Duarte. *MedChemComm* **2016**, *7*, 667−678.

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